Integrated Mendelian randomization and single cell RNA sequencing identify cholesterol gene ABCA1 as a risk factor in oral lichen planus

Te Wang[1,2], Zhi Mao[1], Ping Zheng[3], Min Hu[1,2]*

[1]Department of Orthodontics, Hospital of Stomatology, Jilin University, Changchun, China
[2]Jilin Provincial Key Laboratory of Tooth Development and Bone Remodeling, Changchun, China
[3]Shanghai Pudong New Area People's Hospital, Shanghai, China

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***Corresponding author:**
Min Hu
Department of Orthodontics
Hospital of Stomatology
Jilin University
Jilin Provincial Key Laboratory of Tooth Development and Bone Remodeling
Changchun, China
E-mail: jluwangte@163.com

Oral lichen planus (OLP) is a chronic inflammatory condition that affects the mucous membranes inside the mouth [1]. It is characterized by white, lacy patches, or red, swollen tissues, and can sometimes be accompanied by painful sores or ulcers [2]. The exact cause of oral lichen planus is not fully understood, but it is thought to be an immune-mediated autoimmune condition, where the immune system attacks the cells of the oral mucous membranes [1]. Certain factors may trigger or worsen the condition, including immune system dysfunction [3], hepatitis C infection [4], allergic dental materials [5]. Symptoms of oral lichen planus can vary from none at all to severe discomfort. The most common symptoms include white streaks on the mucous membranes, which are usually painless; red, swollen patches of tissue or open sores, which can cause a burning sensation or pain, especially when eating or drinking spicy or acidic foods; bleeding and irritation when brushing teeth or consuming certain foods and drinks. The severe type would lead to gingivitis or even gum erosion, some types of lichen would also go to malignant pathology [5]. OLP has several different appearances; the most common types are reticular, erosive, atrophic, and plaque-like. The reticular form is the most common and often the least symptomatic, while the erosive and atrophic forms can cause significant pain and discomfort.

The diagnosis of oral lichen planus is usually made by clinical examination, but a biopsy may be needed to confirm the diagnosis and rule out other conditions, including oral cancer [5]. While there is no cure for oral lichen planus, the goal of treatment is to reduce symptoms and monitor for changes. Topical corticosteroids are commonly used to reduce inflammation and pain [2]. For more severe cases, systemic medications or other therapies may be necessary.

The immune system plays a key role in the pathogenesis of OLP, and the exact mechanisms of how the immune system causes OLP are still unclear, and understanding them may help develop better treatments for this condition [3]. With the advance of single cell sequencing, it is available to analyze the sub-cell clusters. A recent study deciphered the monocyte alterations and revealed the accumulation of T cells in OLP patients compared to healthy controls [6, 7]. However, the peripheral status of immune cells have not been well profiled. Another study showed there

is a causal relationship between pro-inflammatory status of macrophages and OLP, but there is no further mechanism investigated [8].

Recently, Mendelian randomization (MR) analysis has been widely used for drug target development and drug repurposing. MR approach uses genetic variants solely associated with the risk factors of interest as instrumental variables to imitate the random allocation of genetic variants from parents to their offspring, thus overcoming the issues of confounding and reverse causality [9]. However, to date, few MR studies integrating genome wide association study (GWAS) and single cell RNA-sequencing data on OLP have been reported. In this study, we aimed to identify both hub genes as potential biomarkers and related immune cell and metabolite markers for OLP.

Methods. ***Medical ethics.*** In this study, the GWAS data were obtained from the public dataset (IEU website), which included 697 OLP patients and 453,036 healthy controls. We also included 14 in-house OLP patients and the ethics have been approved by the local hospital ethical committee in Jilin University.

Statistical analysis. We lastly validated our results in GEO dataset with ABCA1 mRNA expression. Summary statistics were used to describe continuous variables as mean ± standard deviation or median [interquartile range (IQR)] and categorical data were presented as frequency (%). Analysis was performed using R software. Statistical significance was set at the $p < 0.05$ level.

Supplementary methods. The methods for single cell RNA sequencing data analysis and MR Methods are attached in the supplementary files.

Results. ***Metabolomics for OLP.*** We first investigated the association between 1408 circulated metabolites and the onset of OLP. The detailed list of these metabolites is included in Supplementary Table SI. We found that 19 metabolites are positively associated with oral lichen planus and 26 metabolites are negatively associated with oral lichen planus (Figure 1). Among them, we chose the cholesterol level for further analysis, which has the highest OR value compared to other metabolites (OR = 0.71).

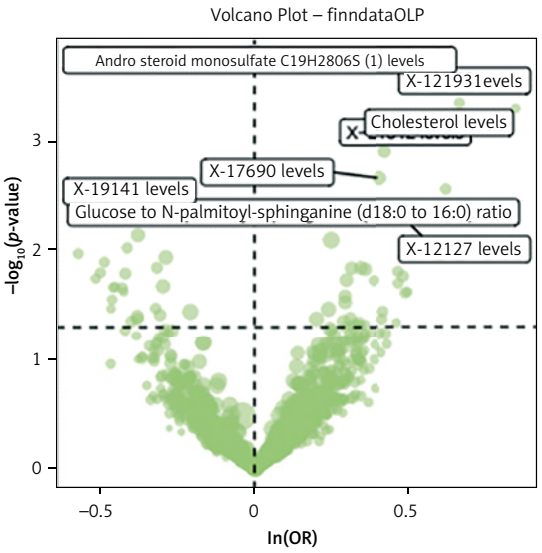

Figure 1. The volcano plot shows the positive and negative relationship between plasma metabolites and the onset of OLP

scRNA-seq study for OLP. To investigate the role of cholesterol in OLP, we applied the analysis of single cell RNA sequencing from GEO dataset (GSE211630) which included one normal, three NEOLP and two EOLP patients, and found 10 cell clusters in oral mucosa in erosive OLP patients, non-erosive OLP patients and healthy controls. Among them, we found increased monocytes in EOLP and NEOLP compared to healthy controls (Figure 2 A). We then located the cholesterol related genes in the single cell analysis. We first found that the cholesterol synthesis genes are mainly expressed in monocytes, neutrophils and smooth muscle cells. Among them, ABCA1 in monocytes have the highest expression (Figure 2 B). Accordingly, we found that the cholesterol receptor gene such as CD36 and STARD4 are mainly expressed in monocytes as well (Figure 2 C).

In addition, we found that the cholesterol receptor gene, import gene, storage gene and efflux gene are more obvious in erosive OLP and non-erosive OLP (Supplementary Figure S1 A). And the cholesterol receptor genes are mostly enriched in monocytes (Supplementary Figures S1 B, C). Meanwhile, the expression of ABCA1 is highly increased in receptor-high monocytes compared to receptor-low monocytes after we classified the monocytes based on the mean expression of cholesterol receptor genes with Addmodule Score methods (Supplementary Figures S1 D, E).

Functional analysis. We then performed the GSVA analysis between the receptor-high and receptor-low monocytes based on the DEGs, and found that the up-regulated genes are mostly enriched in sterol transport, lipid location, cholesterol efflux cholesterol storage and sterol transport; while the down-regulated genes are enriched in lymphocyte-mediated immunity, leukocyte-mediated immunity and chromosome segregation. This indicated that the cholesterol receptor-high monocytes are indeed related to the cholesterol transport; while receptor-low monocytes are involved in impaired immune function (Supplementary Figure S2 A).

Then we sub-clustered the monocytes and identified 12 subclusters. We found that cholesterol receptor genes are mostly expressed in monocytes and ABCA1 is also enriched in some subclusters (Supplementary Figures S2 B–F). To

investigate the role of ABCA1 in monocytes, we applied the RNA velocity analysis and found that most low-expressed ABCA1 monocytes are differentiating into high-expressed ABCA1 monocytes, which confirmed the role of ABCA1 in monocytes in the molecular mechanism of oral lichen planus.

Validation of the study. Then, we applied the public dataset (GSE52130) which included 7 OLP patients and 7 control oral epithelium to validate the expression of ABCA1 in the disease and we found that patients with OLP have higher expression of ABCA1 in oral mucosa compared to healthy controls (Supplementary Figure S2 G, $p = 0.007$). In addition, the plasma cholesterol level is increased in OLP patients compared to healthy controls ($p = 0.0082$, Supplementary Figure S2 H).

The genetic association between ABCA1 and OLP. Lastly, we explored the genetic association between cholesterol genes and OLP. First, we obtained the different expressed genes related to cholesterol receptor from MSigDB website and found DEGs as: 128 increased and 155 down-regulated genes with absolute logFC>1. Among them, ABCA1 gene has the least p-value (Supplementary Table SII). In addition, we applied the eQTLs of each DEG to associate with OLP FinnGen GWAS

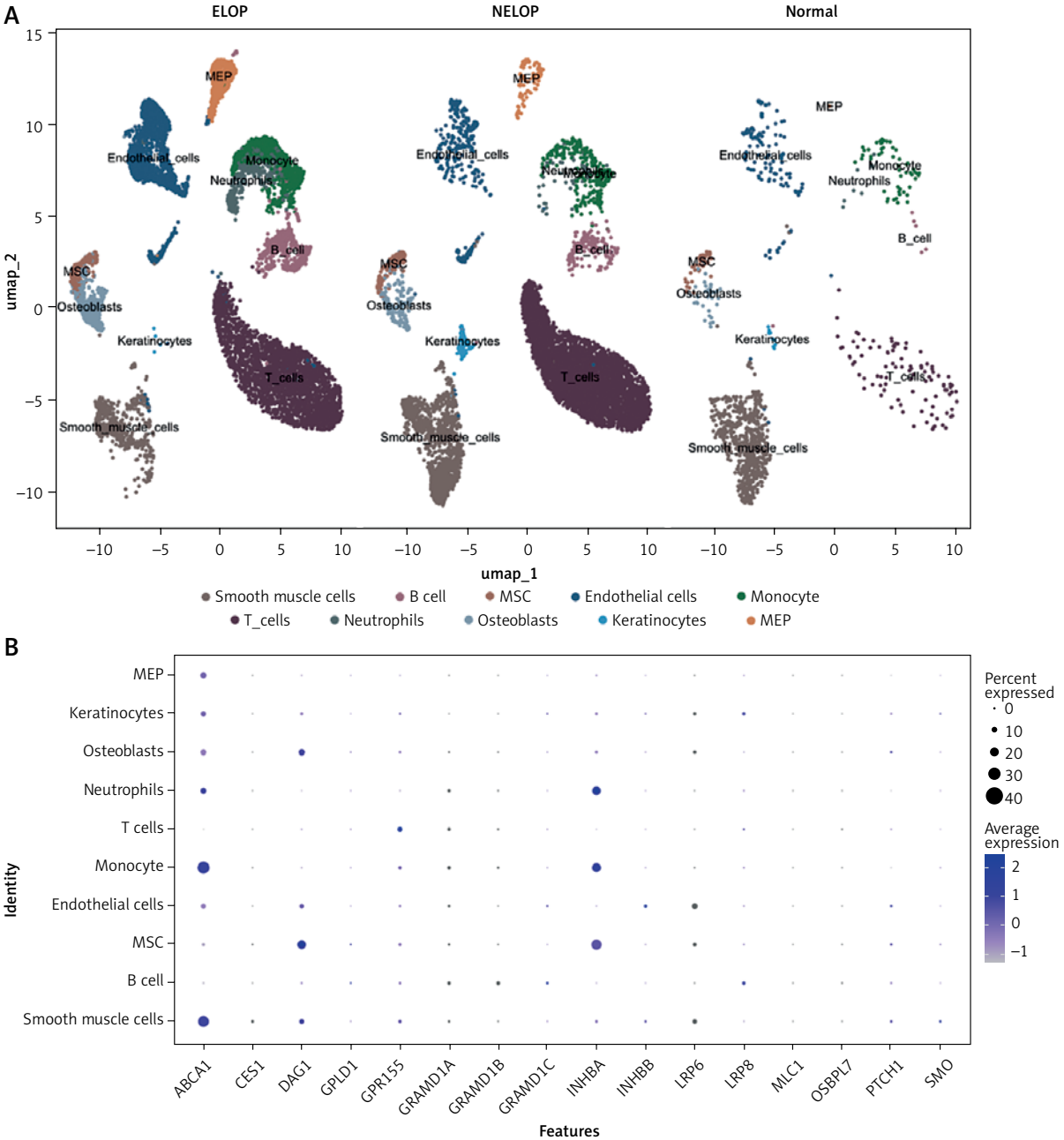

Figure 2. The single cell analysis of the cholesterol related genes in OLP. **A** – The cell annotation of different clusters between healthy controls, non-erosive and erosive OLP patients. **B** – The expression of cholesterol-related genes in cell clusters

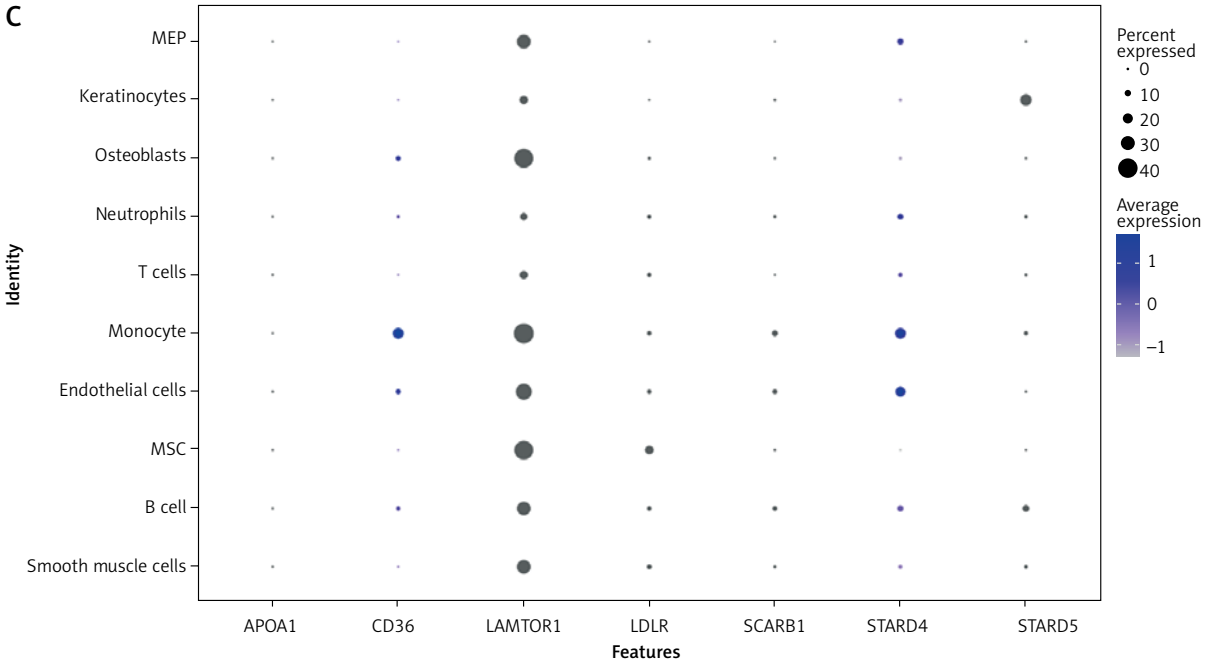

Figure 2. Cont. **C** – The expression of cholesterol-receptor genes in cell clusters

which includes 3323 OLP patients and found that ABCA1 is a risk gene for OLP with OR (1.295: 1.064–1.576, Supplementary Figures S3 A, B).

Discussion. The relationship between cholesterol and OLP is not clearly established and is somewhat complex, involving various factors such as metabolic disorders and systemic inflammation. There is some evidence to suggest that OLP may be associated with metabolic syndrome [10], which is a cluster of conditions that occur together and increase the risk of heart disease, stroke, and type 2 diabetes. These conditions include increased blood pressure, high blood sugar, excess body fat around the waist, and abnormal cholesterol levels. People with metabolic syndrome may have systemic inflammation, which could potentially contribute to the development of inflammatory conditions like OLP. Dyslipidemia, a condition where there are abnormal amounts of lipids in the blood, is also considered a component of metabolic syndrome. Since OLP is thought to have an autoimmune and inflammatory component, dyslipidemia might contribute to or exacerbate the inflammatory state that is believed to play a role in OLP [11].

Some medications used to treat high cholesterol [12], such as statins [13], have been associated with a variety of skin reactions [14]. In rare cases, these drugs can induce lichenoid drug reactions, which are clinical and histological imitations of lichen planus [15]. However, it is important to note that these reactions are not common and the benefits of statins in reducing cardiovascular risk generally outweigh such risks. In addition, the underlying mechanism is not clear and some reports show that antihyperlipidemic drugs can alter T-cell function [14] and cause autoimmunity and atorvastatin can induce OLP by binding to mucosal proteins [15]. And these immune mechanisms seem not to be associated with cholesterol.

Both high levels of cholesterol and OLP are associated with inflammation. Chronic inflammation is a key feature of OLP, and high cholesterol, particularly low-density lipoprotein (LDL) cholesterol, can contribute to atherosclerosis, which is an inflammatory condition. The systemic inflammation associated with high cholesterol might potentially influence the development or severity of OLP [16]. There is also a possibility of a shared pathophysiological mechanism between OLP and certain autoimmune diseases [17]. Since dysregulated lipid metabolism has been implicated in some autoimmune diseases, and considering that OLP has an autoimmune component, there might be an indirect connection between altered cholesterol metabolism and OLP [18].

In our study, we identified the critical role of ABCA1 in OLP by showing that (i) ABCA1 is relatively higher expressed in patient plasma with OLP/plasma of the OLP patient; (ii) ABCA1 is dominantly expressed in monocytes. Therefore, ABCA1 plays a role in the development of monocytes in OLP. However, the exact role of ABCA1 in OLP needs to be explored in *in-vitro* and *in-vivo* disease models. As the single cell RNA seq data has a very small sample size, we had to admit the limitation of the statistical power. Therefore, we used the GEO buld-RNA seq data (which included 7 OLP patients and 7 healthy controls) to further validate our results. In addition, the analysis is based on the European ancestry, which may

reduce the applicability of the findings to other ethnic groups with different genetic backgrounds. It would be essential to investigate the genetic link between cholesterol-related genes and OLP in Asia and African population as well and added essential *in-vitro* and *in-vivo* experiments in the future study. However, our genetic finding only demonstrates that ABCA1 contributes to OLP, and we have not formally demonstrated that ABCA1 activity alone is sufficient to trigger OLP. Thus, while ABCA1 appears necessary, additional factors are likely required and causality remains to be established. In addition, rescue experiments with gain-of-function ABCA1 mutants or cell-specific inducible knock-in studies will be required to establish a direct causal link.

Regarding the metabolic aspect, we found cholesterol receptor alterations in monocytes. We then used MR method to find that most cholesterol level has a positive effect on OLP, which indicated that reducing of the lipid level might be useful to prevent OLP. Our findings suggest that further studies regarding the cholesterol level in relation to immune status may shed light on novel therapeutics.

In conclusion, we demonstrated that ABCA1 plays an important role in the pathogenies of OLP and that targeting ABCA1 may represent a promising new therapeutic candidate in the prevention of OLP in clinical session/practice.

Availability of data and material

All GWAS summary statistics analyzed in this study are publicly available for download by qualified researchers. The GWASs for hub genes can be obtained through the IEU data portal (https://www.thessgac.org/). The GWASs for OLP were provided by the IEU data portal (https://www.med.unc.edu/pgc). All data generated in the current study can be obtained from the Supplementary Material.

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Ethical approval

In this study, we do not use human or animal tissues and the ethics were exempted. We used public dataset from IEU website and GEO websites. All data are available to download freely.

Conflict of interest

The authors declare no conflict of interest.

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